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ABSTRACT

The increasing use and abuse of a variety of drugs have resulted in the nationwide growth of many programs for the detection and treatment of drug abuse. The purpose of developing drug detection methods has been to provide physicians, therapists, and others involved with drug users an objective means to determine and measure drug usage. This report provides an indepth look into the background of such methods of detection and reviews those in current use. (Author/PC)

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The National Clearinghouse for Drug Abuse Information recognizes the need for clarifying some of the more complex issues in drug abuse by gathering the significant research on each subject and summarizing the major findings on various aspects of the problem. This fact sheet was researched by Wesson Associates under Contract No. HSM-42-72-99. Additional recent information was obtained from a monograph published by the Special Action Office for Drug Abuse Prevention entitled "A Guide to Urine Testing for Drugs of Abuse." The following report is intended to give the general public an overview of the subject of detection of drugs in body fluids. Professionals and specialists in this area who desire more detailed, technical information should read the monograph published by SAODAP. Copies of the monograph are available upon request from the National Clearinghouse for Drug Abuse Information.

METHODS FOR THE DETECTION OF DRUGS OF ABUSE IN BODY FLUIDS: AN OVERVIEW

The increasing use and abuse of a variety of drugs has resulted in the nationwide growth of many programs for the detection and treatment of drug abuse. This has created a demand for reliable, rapid and inexpensive methods to accurately detect and identify drugs in body fluids such as urine, saliva and blood. The purpose for development of drug detection methods has been to provide physicians, therapists and others involved with drug users an objective means to determine and measure drug use. Such detection methods may be used for various medical, industrial, social and legal purposes. One important example, which has greatly influenced the development of new techniques, is the mandatory testing of participants in federally-supported treatment and rehabilitation programs. Government regulations require that all individuals enrolled in methadone programs must be tested for morphine once each week and methadone once each month. These tests are performed first to aid in the diagnosis of heroin addiction and determine the suitability of methadone for treatment, and then to monitor the patient's progress toward the goal of discontinuing heroin use.

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Industry is also interested in detection methods since many firms have established programs to screen job applicants for drug abuse prior to hiring them. And, of course, the implications for law enforcement programs range from the detection of drugs as the cause of traffic accidents to the monitoring of ex-addicts in prison and on parole.

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The mass screening of large population groups in high drug use areas, such as the routine testing of servicemen in Vietnam, is based on the communicable disease concept of addiction. Early detection and treatment are emphasized to prevent an increase in addiction.

Although there are many useful applications for methods for detection of drug use, there are also some limitations. With all the advances which have been made in the last few years, methods currently available and suitable for large scale use still cannot detect some drugs, including LSD and marihuana. In addition, test results are often inaccurate, producing false positives or false negatives. (A false-positive result is one which indicates the presence of a drug when the drug has, in fact, not been used. A false-negative result indicates that the drug is not present when it actually has been used.) Also, a positive test result only indicates drug use which may have been one time only; it does not necessarily indicate that the person is addicted. Test results provide useful information but they should be kept in perspective. In the area of testing for drug abuse related to automobile accidents, no widely accepted standard is available for determining the legal intoxicating blood levels for most drugs. Another issue is that mass screening of large population groups may be regarded as a protection of public health or as an invasion of privacy. Many people feel that body fluids are personal and view the obtaining of specimens as a violation of the rights against self-incrimination. In order to protect individual rights, the authority for setting up such programs lies with local institutions such as schools, businesses and voluntary treatment programs rather than with the Federal Government.

Background

One of the first clinical tests developed for the purpose of drug detection was the nalorphine pupil test introduced by J. G. Terry and F. L. Braumoeller in 1955. Although the test is relatively simple to perform, it is limited in that it will detect only narcotics, does not measure quantities of drugs present, and does not distinguish between various narcotics. Uncertain results are also common. Most detection methods in current use today use body fluids for drug analysis. Body fluids which may be used are gastric contents, saliva, blood, perspiration, and urine. The first four may be used providing the specimen is obtained within a relatively short time after ingestion. Blood is used for a variety of tests, particularly with hospitalized patients. It is particularly useful when quantitative levels of drugs need to be determined. Detection methods using blood require sterile blood-collection equipment and technically competent personnel. They are generally unsatisfactory for screening large groups of people, particularly if frequent tests are mandatory. Urine is presently the most convenient source of material for drug abuse detection. It can be obtained in adequate quantities without discomfort, and repeated testing presents fewer problems. The main problem is the

possibility of substitution unless the samples are obtained under observation -- which presents an invasion of privacy. However, chemical analysis of urine is presently the predominant technique used in drug abuse screening programs.

Methods in Current Use

Methods currently available for mass screening of drugs of abuse in urine can be broadly categorized as follows: thin-layer chromatography (TLC), gas-liquid chromatography (GLC), spectrophotometry, and immunoassays. These methods vary greatly as to their suitability for use in large-scale screening programs. Some of the criteria by which a method should be judged are: (a) rapidity of analysis, (b) convenience, (c) economy, (d) sensitivity and (e) specificity. One definition of sensitivity refers to the minimal concentration of a drug or metabolite that can be detected, expressed in units of amount -- micrograms (mcg.) or nanograms (ng.) -- per milliliter (ml.) of undiluted urine. (A metabolite is a substance produced by the process of metabolism in the body; for example morphine is a metabolite of heroin.) The term specificity refers to the degree to which a test can discriminate between closely related drugs or metabolites.

The requirements of a clinical program for drug detection depend on the particular needs and goals of the program. For example, programs that use testing procedures as a deterrent to drug use are usually far more concerned with accuracy and elimination of false positives than programs that use results primarily to evaluate the progress of voluntary patients in treatment programs, or to evaluate different treatment methods. Programs which deal with narcotic users who do not usually abuse other drugs are less concerned about detection of barbiturates and amphetamines. However, in treatment programs where many patients are taking prescribed tranquilizers or antibiotics, the detection method used must be sensitive, accurate, and capable of differentiating prescribed drugs and their metabolites from illicit drugs and their metabolites. In some situations economy may have to be sacrificed for rapidity of analysis, but in treatment or screening programs where time is not a critical factor and where detection of a wide range of drugs is desired, a low-cost, versatile detection method would be preferable.

Thin-Layer Chromatography (TLC)

At present, TLC is the most commonly used method for large scale screening of urine for drugs of abuse because it meets the following criteria: (a) minimum instrumentation, (b) low cost, (c) relative simplicity, (d) minimum laboratory space, (e) moderate rapidity, (f) excellent resolution of components, (g) reasonable sensitivity to a wide variety of abused drugs, (h) specificity, and (i) ease of interpretation of results by laboratory personnel with minimal formal training.

With the TLC method it is possible to detect a wide variety of drugs in a single run. Analysis of a urine specimen by TLC alerts the clinician immediately as to the

number of drugs present in the specimen. In addition, the method can be easily adapted to the purpose of screening, e.g., screening of patients in a treatment program for specific drugs of abuse, or pre-employment screening for a variety of abused drugs. The TLC method can differentiate illicit drugs and their adulterants from legitimate and prescribed drugs and their metabolites. TLC screening methods reliably detect the presence of these drugs or their metabolites in the urine in concentrations of 1 to 3 mcg./ml. of urine. The results are qualitative only; that is, they provide only a yes/no, or negative/positive result.

There is no universally accepted procedure for TLC. There are many different ways the tests can be performed and each has some advantage or disadvantage over other variations. Despite the individual variations there are three steps which are fundamental to all TLC procedures: sample preparation, separation of drugs, and detection. Before the sample can be chromatographed, it must first be processed to isolate and concentrate the drugs from the impurities in whole urine. This step is called extraction. Additional steps such as adjustment of the pH. or evaporation of the sample may also be necessary. Another aspect of sample preparation is the addition of a hydrolysis step. Hydrolysis of the sample converts certain conjugated drug metabolites to free drug (e.g., morphine glucuronide to morphine). This is usually necessary because the water soluble conjugates are not easily extracted in the usual methods of sample preparation. Because all of these steps are time-consuming and complicated, there is currently considerable research activity designed to simplify sample preparation.

The second basic step in chromatography is separation of the drugs. In TLC this involves "spotting" a small amount of the sample on a plate which has been coated with a thin layer of solid support phase, usually silica gel. One edge of the plate is then placed in a solution (the solvent) and by capillary action the solvent slowly moves across the plate in a uniform manner. As the solvent passes over the sample it carries the drugs along with it. The separation is achieved because different drugs migrate or travel different distances from the starting point. The detection step involves spraying the plate with chemicals (reagents) which produce colored spots where each drug has migrated. Each plate can accommodate several samples as well as standard solutions known to contain the drugs. By comparing the distance the known drug migrates to the distance the unknown drugs migrate, identification is achieved. If no drug is present in the sample, no spot appears.

The TLC techniques developed by Davidow et al. (1968), Dole et al. (1966), and Mule (1969) are the ones most commonly used in monitoring treatment programs.

Kaistha and Jaffe (1972) reported the total cost of setting up a toxicology laboratory facility in a drug abuse screening program using the TLC method as $4,328. They also calculated the cost per test for opiates and amphetamines as $1.26, calculated on the basis of 300 urine specimens per week per technician. When a barbiturate analysis is desired along with opiates and amphetamines, it costs an additional 48 cents per specimen. This estimated cost per test included chemicals and other supplies, laboratory rental and overhead, labor costs, and salary for a qualified supervisor.

Gas-Liquid Chromatography (GLC)

Another chromatographic method, GLC, is often used to verify the findings made by TLC. Although the sensitivity of GLC can be made greater than that of TLC, it is usually more time-consuming. GLC, like TLC, permits simultaneous screening for a variety of drugs. The disadvantage of GLC is that only a single specimen can be run at one time. With GLC, a single specimen may require 20-30 minutes for the complete screening of amphetamines and opiates. In the same time interval 12-15 different urine specimens can be tested for a wide variety of drugs on a single thin-layer chromatographic plate.

GLC involves the same three basic steps as in TLC: sample preparation, separation of drugs, and detection. The separation step in GLC differs from TLC in that the sample is injected into a gas chromatograph instrument and volitalized. The drug, in a gaseous state, is forced through a column by a carrier gas. The column usually has a small internal diameter and is loosely packed with an inert solid support coated with a liquid. The principle of separation is based on the partitioning of the drug between the liquid phase and gaseous phase. Thus a mixture of compounds are separated and reach the detector at different times. The time it takes for each drug to pass through the gas chromatograph is different and characteristic for a particular drug. The detector usually makes a graphic representation on a recorder which shows a spike each time a drug strikes the detector. The graph also indicates the retention time of the drug in the instrument and therefore provides identity of the drug.

The initial costs for setting up a toxicology laboratory using GLC are higher than for TLC. A gas chromatograph with one column costs between $5,000 and $10,000. The high initial cost of GLC is partially balanced by the low materials cost per sample. One advantage of GLC is that, unlike TLC, it can be used to provide quantitative results (amount of a drug present in a particular sample) if such information is needed.

Scientists and medical technologists who are interested in practical details about GLC are advised to refer to the Handbook of Analytical Toxicology by Sunshine (1969) and other references cited.

Dr. D. H. Catlin of UCLA states that the primary disadvantage of both TLC and GLC is the lack of sensitivity, particularly in the analysis of morphine where a sensitivity less than 1.0 mcg./ml. is desirable in order to obtain positive results for a reasonable time following heroin administration. This problem can be partially solved by hydrolysis and other sample manipulations but these steps add to the complexity of the procedure. For analysis of amphetamines and barbiturates sensitivity requirements are much less rigid and consequently TLC and GLC are quite suitable. One of the principal advantages of TLC and GLC is that they are capable of detecting all of the drugs commonly abused. Recently they have been used in conjunction with the immunoassays as a means of confirming or double-checking a sample reported as positive by an immunoassay.

Spectral Methods

Spectrophotometric techniques can be subdivided into the following categories: (a) spectrofluorometry, (b) ultraviolet, visible and infrared spectrometry, (c) atomic absorption spectrophotometry, and (d) mass spectrometry. All of these techniques have widespread use in pharmaceutical research as well as in the broad area of organic and inorganic analysis. However, most of these techniques are not widely used in large scale drug abuse screening programs because they lack simplicity and rapidity or they are too expensive. Only fluorometry, also called spectrophotofluorometry, has been commonly used as a method for detection of drugs of abuse in urine.

Spectrophotofluorometry (SPF)

The principle of this method is based on the fact that many drug derivatives known as drug fluorophores emit fluorescent light under specific conditions. The sample is introduced into the instrument and a beam of light at a certain wavelength is directed through the sample. This causes the fluorophore to emit light at another specific wavelength which is detected by a photocell. Before the sample can be placed in the fluorometer, the drug must be extracted from the urine to eliminate urine elements which may interfere with the analysis. The extracted drug is then converted to a fluorophore by a chemical reaction.

There are two major commercial instruments presently available which apply this methodology and are suitable for mass screening. The Farrand Optical Company in New York markets an automated turret SPF which permits semi-automation, and Technicon Instruments Corporation of Tarrytown, New York, has developed a fully automated SPF system for morphine. Both the Farrand and Technicon systems have been designed and marketed with the specific purpose of detecting morphine in urine, although methods are available for the analysis of many other drugs of abuse and any spectrophotofluorometer could be used for that purpose. Since the Technicon instrument is automated, however, major revisions would be required to detect drugs other than morphine. Both systems are relatively rapid. Using the Farrand system one technician can process 400-500 samples per 8-hour shift. Using Technicon one technician can process 200-350 samples per 8-hour shift. The initial cost of the Farrand system is in the range of $6,000 for a single unit, and cost per test is approximately $1.07. The initial cost of the Technicon instrument is $25,000, and cost per test is approximately 27 cents. SPF can be used in either a high or low volume operation. Some laboratories use it on all samples and do not confirm the positive results, others confirm results by another method. It is also used for confirming a positive result obtained by immunoassay. The required sample preparation, which should include hydrolysis, and the relatively high cost place limitations on the Farrand system. The Technicon system is not widely used because of the very high initial cost and some instrument maintenance problems.

Immunoassays

The most recent developments in the detection of drugs are the tests which use immunochemical techniques. These tests show particular promise because of their relative simplicity, rapidity and adaptability to high volume. They do not require preliminary sample processes such as hydrolysis and extraction. On the other hand, they are less specific than TLC and GLC, and the cost of the necessary chemicals (reagents) for a single analysis is relatively high. All of the immunoassays for drugs are less than 3 years old and some have been available for only several months. New reagents and variations in the general procedure are rapidly becoming available. Most of the experience to date has been with the morphine test although tests for methadone, barbiturates, amphetamines and cocaine are now available. At the present time critical data evaluating and comparing the tests are relatively sparse.

One of the main advantages of the immunoassays is sensitivity. Compared to the older methods, specificity is not good and is the main disadvantage. In these tests sensitivity and specificity are necessarily interrelated--the more sensitive, the less specific and vice versa. Because of the high sensitivity of immunoassays, the results, if properly interpreted, may give significantly longer time courses of detection following human drug administration than the older methods.

A positive result by immunoassay must be either cautiously interpreted or confirmed by another more specific test. A negative result, however, can be interpreted as very strong evidence that the drug is not present. Because of the excellent sensitivity of these tests, an additional interpretation of a negative result is that the drug has not been used for several days. In practice this means that immunoassays are excellent screening techniques where the emphasis is on high volume, sensitivity, and simplicity, and less emphasis is placed on specificity. Any situation where a high percentage of the samples will be negative and the few positives can be confirmed is particularly suitable for immunoassay.

Four different tests are currently commercially available: the free radical assay technique (FRAT); the enzyme multiplied immunoassay technique (EMIT); the radioimmunoassay (RIA); and the hemagglutination inhibition assay (HI). The major advantages and disadvantages of each of these tests are indicated in the remainder of this report. Readers who are interested in technical information about the tests are referred to the sources cited at the end of this paper.

FRAT

The FRAT test was introduced by Syva Corporation of Palo Alto, California in July 1971. It has been used extensively by the military to test homebound soldiers from Vietnam for drug abuse, when rapidity was essential. The major disadvantage of FRAT is the high initial cost, since the required spectrometer costs $27,000. The Syva Corporation estimates the cost of one assay for one drug to be approximately

55 cents. The major advantage is that if the instrument is warmed up (after 30 minutes) a single result can be obtained in one minute. For this reason FRAT is particularly well suited for those situations where a result is needed in a very short period of time. The high incidence of false positive results requires that another test must be used to confirm a positive FRAT result. In recent months the Syva Corporation has been placing more emphasis on their new test called EMIT, a homogenous enzyme immunoassay technique.

EMIT

EMIT was introduced in the fall of 1972 by Syva Corporation. Reagents for morphine, amphetamines, barbiturates, cocaine and methadone are available. Several laboratories are evaluating the system and initial reports are encouraging. Syva reports that the sensitivities are the same as in the FRAT system. As with all the other immunoassay techniques, positive results must be confirmed with another test. Like the FRAT, a single test requires about one minute. Laboratories evaluating EMIT report that one technician can perform 200 assays in one 8-hour shift. The system is used with a clinical spectrophotometer coupled to a desk calculator modified to act as a printer. The initial investment for a spectrophotometer is estimated to be $7,500 as compared to the $27,000 cost of the FRAT instrument. The estimated cost of one assay is 75 cents. The method should lend itself well to automation.

Radioimmunoassay (RIA)

The RIA was originally described by Spector et al. (1970) and was marketed by Hoffman-LaRoche in November 1972 as the Abuscreen. It is now marketed utilizing either tritium (^{3}H) or iodine (^{125}I). The tritium test was evaluated by Catlin et al. (1973) and by Gorodetzky et al. (1972). More laboratories have begun to use the test but it is too early for general evaluation. The RIA is more sensitive than FRAT or EMIT. There is evidence that the increased sensitivity will permit detection of low single doses of heroin as long as several days. The Abuscreen system is used with a liquid scintillation spectrometer or gamma counter costing a minimum of $6,000. A centrifuge is also required, which costs between $500 and $1,000. Average costs per test range between $.65 and $1.40 according to volume. The Abuscreen is most suited for high volume situations where automation is important. Partial automation is available but adds considerably to the initial costs. The excellent sensitivity and low incidence of false positives are most suitable for screening situations where another test is used to confirm results. The high costs and present limitation to detection of only morphine are disadvantages. In addition, since radioactivity is used there is an element of health and environmental hazard.

Hemagglutination Inhibition (HI)

The hemagglutination inhibition test for morphine was first described by Adler et al. (1971). The commercial version of the test was developed and marketed in November 1972 by Materials and Technology Systems, Inc. in Chicago. It is currently marketed by R. D. Products, Inc., Box 3, New York under the name of

HI-M Test. Subsequent to the original publication Adler et al. (1972) described a modified version of the test and included data on its reproducibility and accuracy. At the present time it is being used by a number of laboratories but it is too early to draw definite conclusions regarding its usefulness. Because of its advantages of simplicity and low cost, it will undoubtedly receive widespread evaluation. The hemagglutination inhibition technique itself is not new. What is new is the application of the technique to detect drugs such as morphine. Because of its simplicity a moderately skilled technician can learn the technique in one or two days. One technician can perform 400 tests per 8-hour shift. One of the most significant advantages of this test is that no expensive or complicated equipment is required. The initial costs are $100 - $200 for the purchase of a simple centrifuge and a few pipets. Costs per test range between 20 and 35 cents. The combination of low cost and high sensitivity make the test suitable for high or low volume programs. The lack of specialized equipment makes the test relatively easy to transport from one location to another. Disadvantages are that the test is limited to morphine at the present time, and there is no provision for automation.

The National Clearinghouse for Drug Abuse Information does not endorse or recommend the commercial products discussed in this report. Most of the research and development in this area is being performed by private industry, and the state of the art is rapidly changing. The Clearinghouse is interested in keeping abreast of new developments and recognizes the need for future reports on this subject as new information becomes available.

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